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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,674	10/30/2001	Hiroaki Yamamoto	06501- 092001 / D1-A0009-	1427
26161	7590	03/19/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			PAK, YONG D	
		ART UNIT	PAPER NUMBER	
			1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,674	YAMAMOTO ET AL.	
	Examiner Yong D Pak	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 19 December 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 5-7 and 10-50 is/are pending in the application.
 - 4a) Of the above claim(s) 5-7 and 10-23 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 24-29, 31-32, 36-37 and 39-50 is/are rejected.
- 7) Claim(s) 30,33-35 and 38 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

The amendment filed on December 19, 2003, canceling claims 1-4 and 8-9 and adding claims 24-50, has been entered.

Claims 5-7 and 10-50 are pending.

Election/Restrictions

Claims 5-7 and 10-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-29 and 39-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 28-29 are drawn to a (R)-2,3-butanediol dehydrogenase having the enzymatic and physical properties listed in the claim. Applicants argue that the characteristics recited in claim 28 clearly limit the claimed genus of polypeptides to those having very similar structure and function. The examiner disagrees.

Claim 28 is drawn to a genus of (R)-2,3-butanediol dehydrogenase, with any structure and from any source. Even though claim 29 limits the source of the (R)-2,3-butanediol dehydrogenase to the genus of *Pichia*, the specification only teaches one representative species, SEQ ID NO:2, from *Pichia angusta* having the properties recited in claim 28. One representative species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of a *P. angusta* (R)-2,3-butanediol dehydrogenase and the structure of a (R)-2,3-butanediol dehydrogenase from another source. Therefore, the specification fails to describe other representative species of the genus of (R)-2,3-butanediol dehydrogenase having the properties listed in claim 28.

Claims 39-50 are drawn to (R)-2,3-butanediol dehydrogenase comprising SEQ ID NO:3, 4, 5, which are 10, 21 and 5 residues in length, respectively. Applicants argue that the since SEQ ID NO:3, 4, and 5 are fragments of SEQ ID NO:2 and the claims recite a function, the claims meet the requirements of written description. The examiner disagrees.

The genus of polypeptides that comprise these above fragments of SEQ ID NO:2 is a large variable genus with the potentiality of encoding many different proteins. Therefore, many structurally unrelated polypeptides are encompassed within the scope of these claims. A description of only 5-20 amino acids, which represent 1-5% of the whole structure of SEQ ID NO:2, amount to insufficient description of the structure of the polypeptides in these claims. Although claims 41, 44, 47 and 50 limit the claims to a (R)-2,3-butanediol dehydrogenase derived from *Pichia*, the specification only teaches

one representative species, SEQ ID NO:2, from *Pichia angusta*. Also, even though claims 40, 43, 46 and 49 are drawn to a (R)-2,3-butanediol dehydrogenase with a specific activity of 100 U/mg or higher, this description is not sufficient to describe the structure of the (R)-2,3-butanediol dehydrogenases because the specific activity of a protein is a measure of its purity. Therefore, the specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being a (R)-2,3-butanediol dehydrogenase and fails to provide any structure: function correlation present in all members of the claimed genus.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 28-29 and 39-50.

Claims 24-29, 31, 32, 36, 37 and 39-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the (R)-2,3-butanediol dehydrogenase of SEQ ID NO: 2, does not reasonably provide enablement for (R)-2,3-butanediol dehydrogenase of unknown structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir., 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims encompass molecules having very low structural similarity to SEQ ID NO:2 that exhibit (R)-2,3-butanediol dehydrogenase activity. The structural limitations are as follows: 70-95% of the whole structure of SEQ ID NO:2 and a (R)-2,3-butanediol dehydrogenase of undefined structure. Despite knowledge in the art for the isolation of amino acids, the specification fails to provide guidance regarding how to isolate other (R)-2,3-butanediol dehydrogenase whose sequence is different from SEQ ID NO:2. Therefore, the breadth of these claims is much larger than the scope enable by the specification.

The predictability as to the level of conservation between the disclosed sequences and those of other (R)-2,3-butanediol dehydrogenase is extremely complex. While recombinant techniques are available, it is not routine in the art to screen large numbers of amino acids where the expectation of obtaining similar sequences is unpredictable. The amino acid sequence determines the structural and functional properties of an enzyme. Knowledge of which sequences can be altered or removed and still result in similar protein activity is well outside the realm of routine experimentation.

The specification, as discussed above which places no limit to the source or structure (R)-2,3-butanediol dehydrogenase, does not support the broad scope of the claims because the specification does not establish: (A) regions of the protein structure which may be modified without effecting (R)-2,3-butanediol dehydrogenase activity; (B)

the general tolerance to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for substitutions, deletions, insertions/additions or multiple modifications, as encompassed by the instant claims. Also, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

Therefore, one of ordinary skill would require guidance in order to make (R)-2,3-butanediol dehydrogenase different from SEQ ID NO:2 in a manner reasonable correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Allowable Subject Matter

Claims 30, 33-35 and 38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned

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are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner

Rebecca Prouty
REBECCA E. PROUTY
PRIMARY EXAMINER
~~L. G. P. 1600~~
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